Lessons Learned from the Registration of Paromomycin in India
24 June 2009
Philippe Desjeux & Louise Johnson

Paromomycin history (1)

• Broad spectrum aminoglycoside antibiotic

• First manufactured in 1959 by Farmitalia Carlo Erba (Italy) as an antibiotic

• Multiple approvals have been granted over the years as an antibacterial

• Generic names include: aminosidin sulfate, aminosidine sulfate, catenulin sulfate, crestomycin sulfate, estomycin sulfate, hydroximycin sulfate, monomycin A sulfate, neomycin E sulfate and paucimycin sulfate.

• Trade names (parenteral) include: Gabbromicina, Gabromicina and Gabromycin
Paromomycin History (2)

- Marketed internationally as a parenteral antibacterial agent and as oral antiprotozoal agent since the 1960's
- (> 40 years)

- Oral and injectable formulations marketed, but only oral formulation still available by the time the Phase 3 clinical trial in Visceral Leishmaniasis (VL) was planned

Paromomycin History (3)

- Late 1980's-mid 1990's: number of pilot clinical trials for safety & efficacy against kala azar with Pharmacia & Upjohn (P&U) donated injectable PM

- 1993-1997: pre-clinical and clinical studies supported by TDR/University of Illinois/SoloPak Pharmaceuticals to expand the dossier

- 1997-today: TDR/IDA developed new liquid filled GMP injectable PM dosage form which was proven to be bio-equivalent to P&U product.

- 2001 Institute for One World Health (iOWH) set up a new partnership with TDR/IDA
Paromomycin: Project Objectives

- To produce a safe and efficacious GMP injectable product for VL treatment
- To produce and submit a regulatory dossier that meets international regulatory guidelines
- To produce a GMP finished product to be available in the public sector of VL endemic countries for the lowest cost possible per 21 day treatment course

PM Chemistry, Pharmacy, Pre-clinical & PKs

- Source of GMP drug substance raw material:
  - Antibioticos, Milan, Italy
- Source of GMP drug product
  - Pharmamed Parenterals Ltd (PPL), Malta, for IDA, Amsterdam
  - 500 mg PM sulfate / ml - 2ml
- All tests negative for mutagenicity & genotoxicity
- PKs: HPLC, single dose IM assay to evaluate PM concentration in biological fluids of 16 HNVs at 12 or 15 mg/kg
PM Safety data: use on infectious diseases

- Summary data for 2,397 patients treated with injectable PM for various infectious diseases.
- Up to 2g/day for 30 days
- AEs; hearing function (0.4%), renal dysfunction (0.1%) not age-related
- Japanese data on 2,220 patients
- AEs: injection pain (4.2%), local rash (1.4%)
- High safety profile

PM: Several phase II clinical trials with CRFs

- In India, Kenya & Sudan
- VL randomised controlled trials:
  - PM versus pentavalent antimonials (Sb5+)
  - PM + Sb5+ versus Sb5+ alone
  - Different doses of PM (12 to 20 mg/kg/day for 21 days)
  - >10 clinical trials
GCP Bio-equivalence Study

- To demonstrate the bio-equivalence between the “Old” and “New” formulations of PM
- 16 HNVs randomised to 15 mg/kg of “Old” and “New” formulations
- Higher peak (C max) observed with the PPL Paromomycin product
- Higher peak don’t affect toxicity profile of the drug
- The two products were considered to be bio-equivalent

Phase 3 Clinical Trial

- Conducted in Bihar State, a VL highly endemic region in India
- 667 patients in 4 sites
- Principal investigators (PIs) from KACE were highly experienced leaders in the treatment of VL. They provided guidance in protocol development
- To compare safety & efficacy of paromomycin to standard treatment in the region, amphotericin B in a randomised, open-label, controlled trial
Registration Dossier

- **Summary of international marketing history**, including list of all countries in which paromomycin had ever been marketed

- **Discussion of product withdrawals** with focus on reasons for withdrawal (not safety related)

- **Summary of safety profile**, including Summary of Product Characteristics and reports from the WHO Uppsala Monitoring Centre database

---

Registration Dossier

- **Phase 3 clinical study report** submitted to DCGI

- **Manufacturing information**, with reference to US pharmacopeial monograph for paromomycin active ingredient

- **Summary of nonclinical information**, primarily from the literature

- **Summary of published clinical studies**, including one pharmacokinetic study in humans
### Lessons Learned

- Important to **engage local clinical and regulatory experts before initiating development work**
- Helpful to capitalize on clinical investigators’ and regulators’ recognition of the **need for a new treatment for VL**
- Important to consolidate **extensive information** from previous use in **other indications and in other regions** to provide a thorough discussion of the risks and benefits of the drug
- Important to provide data showing the drug could be used **safely and effectively in the Indian population**

### Additional Registrations

- Registration dossiers in preparation for filing in **Bangladesh and Nepal**
- Rely on **Indian approval** and information from Indian dossier and safety information from recently completed **Phase 4 study (500 patients)** plus **PM inclusion in WHO, EML**
- Several meetings held with governments of both countries to reach agreement on **requirements for timely approval** of an important, new treatment for VL
Thank you!

Dr Philippe Desjeux  
Senior Program Officer for Disease Control  
Institute for OneWorld Health (iOWH)  
899 rue Jean de Gingins  
01220 Divonne, France

Tel: (0033) 4 50 20 44  61
Mobile: (0033) 6 73 52 99 44
E mail: pdesjeux@oneworldhealth.org
http://www.oneworldhealth.org